Amendments to the Drawings

Please amend the drawings by accepting the replacement sheets for Figs. 1, 1A, 2, 3a – 3d, 5a -5c, 6 – 6i, 7 and 8a – 8c as attached to the Appendix where line drawings have been substituted for half-tone drawings and additional and clearer figure legends have been provided. No new matter has been introduced.

REMARKS

Status of Claims

Claims 1 – 64 were original in the application. Claim 40 have been cancelled. Claims 6 – 32, 34 – 39 and 41 – 46 have been withdrawn. Claims 1 – 5 and 33 have been amended in this amendment. Claims 1 – 5 and 33 are submitted for examination on the merits.

Request for Reconsideration of Restriction and Withdrawal of Claims

Prior counsel for applicant elected claims 1 – 5, 33 and 40 as drawn to Apparatus Species II[1] and Communications Link Species I. Claim 1 was asserted as generic. All claims depend on claim 1, which is the single independent claim in the application.

However, elected and examined claim 1 as amended is directed to an implantable apparatus comprising *an implantable pouch*, at least one medicating agent, at least one implantable piezoelectric pump fabricated in the pouch which forms a skeleton of the pump, and an implantable, syngeneic and biodegradable skin covering the pouch and pump. Apparatus Species I was defined in the Restriction Requirement as a device that "contains a synthetic pouch compartmentalized into three or more chambers, and an electronic apparatus controlling and modulating the delivery of the agents to the site of the tumor. There was no explicit reference to a pouch in the definition of Species II, whereas claim 1 appears to fall within the

[1] Species II: The device contains an electronic system providing tailored and controlled regulation of the administration of such agents, using sensors to monitor the progress of the treatment.

scope of Species I. Therefore, it is assumed that search and examination was consistent with the scope of claim 1 and Species I. Examined claims 2 – 5 and 33 include various active or tailored control and regulation elements, or communication links. Therefore, the subject matter of all claims effectively fell within the scope of the actual search and examination.

The applicant respectfully maintains that claim 1 as amended is allowable and generic to all claims and species. All claims depend on claim 1 and are allowable therewith. Hence, rejoinder of the withdrawn claims is requested pursuant to MPEP 824.04.

Objections to the Drawings

Substitute drawings have been responsively submitted.

Amendments to the Specification

The specification and title has been responsively amended.

Rejection Pursuant to 35 USC 112

Claim 3 has been responsively amended. The Examiner's invitation to incorporate structural recitations of the invention into the pending claims is noted.

The Claimed Invention

Consider first the nature of the claimed invention and its differences over Kaiser, then we shall turn to the amended claims in light of these noted differences. Thereafter, we will consider the distinctions made of the proffered rejections.

The claimed invention is directed to:

1. A biodegradable substrate forming the skeleton of the pump, e.g. a skeleton made of collagen matrix.
2. A biodegradable skin cover for the system, e.g. made of Integra®, which is syngeneic, namely does not produce an antigenetic response due to its biocompatibility.
3. A system for dispensing biological response modifiers (BRMs) used as a biotransmitter in a closed loop or homeostatic control mode where control of the operation of the system is performed by the system autonomously with internally defined parameters and a bidirectional multistate switch permitting stability of operation of the system.
4. Self-adjustment of the control with respect to the bio-absorbability, pharmacokinetic and pharmacodynamic parameters of the system as a whole to achieve stability of the homeostatic state as the primary mechanism by which the supply mode of the pump is operated.

Rejection Pursuant to 35 USC 102

Kaiser U.S. Patent 5,569,187

Claims 1 – 5 and 33 were rejected as being anticipated by Kaiser.

AN IMPLANTABLE, BIOCOMPATIBLE AND BIODEGRABABLE INTEGRATION OF A MEDICATION DISPENSING SYSTEM IS A FIRST DISTINCTION OF THE CLAIMED INVENTION OVER KAISER.

The claimed invention is directed in claim 1 for example to a fully implantable, biodegradable pump-and-valve system which is an interactive biohomeostatic system in which the structure of the pump 200 is a virtual additional organ which is biologically integrated with the human organ being treated. The biodegradable pump-and-valve system is rendered biodegradable by manufacture of all the nonelectrical portions of the system out of collagen or some other biocompatible and biodegradable material. For example, in the portion of the specification related to Fig. 6J see the disclosure concerning synthetic skin 143 which is disclosed as a porous matrix of fibers of crossed-linked Bovine tendon collagen, and which is biodegradable when implanted into the subject organ. Various types of implantations are shown and described in connection with Figs. 8, 8a, 8b, and 8c. In the claimed invention the system introduces biological response modifiers such as INF-2, IL-2, TNF, and monoclonal antibodies in a closed loop operation without the necessity of operator intervention.

Kaiser is utterly silent with respect to any issue of biocompatibility, or biodegradability of the implanted chemical supply 6. The implant in Fig. 3 is in fact stated as being made of glass, which is bio-impervious and anything but biodegradable. Implant 6 stays implanted in the patient well after any treatment and remains until death or surgical removal. The limitations in amended claim 1 which render it a virtual organ take it out of the possible scope of Kaiser.

Claims 2 – 5 and 33 each depend directly or indirectly on claim 1.

A CLOSED LOOP BIASING OF THE CLAIMED TUMOR-POUCH MECHANISM FOR LOCAL ADMINISTRATION OF MEDICATING AGENTS IS A SECOND MATERIAL DIFFERENCE OVER KAISER.

The claimed invention is directed in claims 2 – 5, for example, to control of the pump proportional to an internally defined parameter, such as bioabsorbability, serum concentration, or effective dose, thereby resulting in a homeostatically, closed loop controlled system.

As disclosed in paragraph [0007] the claimed invention locally dispenses, controls, regulates medicating agents at the tumor site of a patient. The operation is autonomous and reporting the results of such agents is only optional and not a necessity of operation since there need be no man-in-the-loop. To effect this autonomous operation the monitoring and reporting of biological response parameters are stored in the resident memory of the implantable system. The effective use of the medicating agents (biological response modifiers, enzymes, therapeutic agents, drugs, chemotherapy agents, and the like) arises from a definite local dose and timeline to produce the results of tumor burden elimination or reduction.

As disclosed in paragraph [0010] a parametrically determined optimal biological dose (OBD) as opposed to maximum tolerated dose (MTD) is administered locally as defined by the programmability and logic of the implantable microprocessor using stored look-up-tables, such as the use of empirically determined pharmacokinetic and pharmacodynamic parameters associated with chemotherapeutic agents to achieve the desired results without the toxic side effects by local delivery of the OBD instead of the MTD.

As disclosed at paragraph [0057], the claimed apparatus uses the fact that a tumor is generally locally hotter than its surroundings, a fact that makes the use of the disclosed device able to detect the tumor and chart the progress in its destruction. That is, as the tumor is destroyed its temperature is gradually reduced, until it reaches the temperature of the surroundings. It is the goal of the disclosed apparatus to eliminate the tumor and to be able to continuously monitor the local progress in its treatment.

Kaiser never operates as a closed loop or autonomous system, but takes step by step instructions from an external control circuit 18 and interrogation unit 14. Kaiser is incapable of closed loop or autonomous operation, if for no other reason, it includes no internal or implanted sensors by which its operation could be controlled. The responder 16 of Fig. 2 is shown in detail in Fig. 5 with actuator 10 and tank 12, which comprise all of the implanted elements of chemical supply 6. No sensor is disclosed for any purpose and all command instructions are received from the external control circuit 18 shown in Fig. 4. Kaiser states at col. , line , "Control circuitry 18 provides information to an interrogation unit 14 to control the supply of chemicals." No control of supply of the medication agent is included in responder 16, let alone autonomously controlled by sensed local input as in amended claim 3.

A BIDIRECTIONAL COMMUNICATIONS LINK FOR CONTINUOUSLY REPORTING THE BIO-PARAMETRIC STATUS IS A THIRD MATERIAL DIFFERENCE OVER KAISER.

The claimed invention is directed to a bidirectional communications link which continuously reports the bio-parametric status of the patient-chemical and patient-

biological. As disclosed in paragraph [0011] treatment is improved by the local real time modulation of the output of the medicating agents from the implanted device during treatment through the use of a command structure of the microcontroller look-up-tables and use of a built-in communication link. The rate of dispensation of the medicating agents is modified by control of the duty cycle of the pump.

Kaiser's system is not disclosed as being reprogrammable. While Kaiser does disclose a bidirectional communications line in Fig. 3, there is no disclosed relationship between generation of commands and the state of the patient treatment. Only the amount of dispensed chemical is communicated on the bidirectional communications line in Kaiser. Kaiser's bidirectional communications line is used only as a remote switching means to open and close the actuator or pump 10.

In regard to claim 2 Kaiser teaches at col. 1 that in prior art devices chemical or drug delivery was impaired by noise due to wiring, inaccuracy of input/output relation between the pump mode and the supply needed. The concept of multiplexing (col. 2: 5-10) is dependent on the operator's settings, and not on the homeostatic state of the chemical imbalance and the absorption rate, either "bio-absorbability", "solubility" and other indices which are inherent to the biostability of the homeostatic state of the system.

Kaiser refers only to the supply of chemicals or insulin and never to a system for administering cytokine or chemotherapeutic agents in a combination therapy. Amended claim 4 calls for a control circuit to control the piezoelectric pump to provide for autonomously regulating, controlling, and modulating a combination therapy. Structurally two tanks are required for a combination therapy and a different type of

circuit control is required for *autonomous* operation of the same as opposed to Kaiser's external controller.

Connelly et al. U.S. Patent 6,589,229

Claims 1 - 5 and 33 were rejected as being anticipated by Connelly.

AN IMPLANTABLE, BIOCOMPATIBLE AND BIODEGRABABLE INTEGRATION OF A MEDICATION DISPENSING SYSTEM IS A FIRST DISTINCTION OF THE CLAIMED INVENTION OVER CONNELLY.

As in the case of Kaiser, Connelly is utterly silent with respect to any issue of biocompatibility, or biodegradability of any portion of the device. Connelly is not an implantable device, but is worn by the patient on the outside and infuses insulin into the subcutaneous layers of the skin through a needle. See col. 6, lines 50 – 58. The limitations in amended claim 1 which render it a virtual organ take it out of the possible scope of Connelly.

Claims 2 – 5 and 33 each depend directly or indirectly on claim 1.

A CLOSED LOOP BIASING OF THE CLAIMED TUMOR-POUCH MECHANISM FOR LOCAL ADMINISTRATION OF MEDICATING AGENTS IS A SECOND MATERIAL DIFFERENCE OVER CONNELLY.

Connelly is recognized for showing a piezoelectrically-actuated valve or pump structure used in combination with thermal flow sensors and closed-loop control circuits for providing the desired flow rate control of insulin through the device into the patient.

The control circuit in Connelly is not structured to provide scheduling of the medicating agent in a closed loop control mode so that control of the operation of the system is performed autonomously with homeostatic parameters. No body parameters are measured by any sensor in Connelly to allow for the possibility of homeostatic control. Fig. 21 of Connelly refers to a conventional strip glucometer 280 to provide input data to the microcontroller, which means that the patient performs a skin puncture from some body local other than where the device is located, collects a blood sample onto a strip, and inserts the strip and sample into an external measurement device, which reads the data and then communicates it to an external processor. Again, none of the Connelly device is considered implanted.

Claim 2 is directed to an implanted control circuit to control said at least one piezoelectric pump to provide proper dosing and scheduling of said medicating agent in a closed loop control mode so that control of the operation of the system is performed autonomously with local homeostatic parameters. Reference is again made to the features of paragraphs [0007], [0010] and [0057], discussed above in connection with Kaiser and the distinctions noted there are reincorporated here.

Connelly never operates as a closed loop or autonomous system controlled by local homeostatic parameters, but takes instructions from an external programmer 270 based on flows in the device and not on any body or homeostatic parameters. See col. 21, lines 27 et.seq.

Like Kaiser, Connelly refers only to the supply of chemicals or insulin and never to a system for administering cytokine or chemotherapeutic agents in a combination therapy. Amended claim 4 calls for a control circuit to control the piezoelectric pump to

provide for autonomously regulating, controlling, and modulating a combination therapy. Structurally at least two separate reservoirs are required for a combination therapy and a different type of circuit control is required for *autonomous* operation of the same as opposed to Connelly's single reservoir system.

A BIDIRECTIONAL COMMUNICATIONS LINK FOR CONTINUOUSLY REPORTING THE BIO-PARAMETRIC STATUS IS A THIRD MATERIAL DIFFERENCE OVER CONNELLY.

Connelly has bidirectional communications link between an external programmer and an external insulin pump. There is no communication with an implanted system or body sensors of any kind. Connelly is thus recognized for providing a wireless bidirectional communications link as illustrated in FIG. 21, the communication between the programmer 270 and the drug infusion device 30. Connelly's programmer 270 transmits flow rate settings and other commands to the drug infusion device 30, and drug infusion device 30 transmits confirmation of these settings and commands back to the programmer 270 to preclude the possibility of erroneous operation due to communication errors. The return communication link also allows the drug infusion unit 30 to transmit status information back to the programmer 270 so that it can be displayed to the user on the display screen 274. Such status information may include the actual flow rate of insulin in the device 30, the time or fluid quantity remaining before the reservoir in the disposable portion 32 becomes empty, overflow or underflow alarms, a low battery condition in the reusable controller 34, and similar types of information.

The communication circuit of Connelly solely communicates system related information between the external programmer and the externally worn insulin dispenser. Claim 33 requires an implantable wireless bi-directional communications link coupled to the *implanted sensor* through the control circuit for communication of local homeostatic sensed bio-parameters to an external user. Claim 33 further depends on claim 3 and is allowable therewith.

Gillis et al US Patent Application 2003/0069541

Claims 1 - 5 were rejected as being anticipated by Gillis.

AN IMPLANTABLE, BIOCOMPATIBLE AND BIODEGRABABLE INTEGRATION OF A MEDICATION DISPENSING SYSTEM IS A FIRST DISTINCTION OF THE CLAIMED INVENTION OVER GILLIS.

Gillis is directed to what is disclosed as possibly fully implanted drug delivery device, but Gillis is in the nature of an implantable catheter in which a subcutaneously implanted reservoir 74 is communicated through a catheter 60 to provide a medication at the distal end 62 at a delivery site. While the guide 10 is described as being biocompatible, it is not described as biodegradable in whole or part. There is no disclosure of an implantable, syngeneic and biodegradable skin covering the pouch and pump as required by claim 1. The limitations in amended claim 1 which render it a virtual organ take it out of the possible scope of Gillis.

Claims 2 – 5 and 33 each depend directly or indirectly on claim 1.

A CLOSED LOOP BIASING OF THE CLAIMED TUMOR-POUCH MECHANISM FOR LOCAL ADMINISTRATION OF MEDICATING AGENTS IS A SECOND MATERIAL DIFFERENCE OVER GILLIS.

Gillis is not directed to any closed loop biasing system for controlling administration of drugs. In fact at paragraph [0120] Gillis states:

> [0120] Release of drug from the reservoir, particularly controlled release of drug from the reservoir, can be accomplished in any of a variety of ways according to methods well known in the art, e.g., by incorporation of drug into a polymer that provides for substantially controlled diffusion of drug from within the polymer, incorporation of drug in a biodegradable polymer, providing for delivery of drug from an osmotically-driven device, etc. Drug can be delivered through the drug delivery catheter to the treatment site as a result of capillary action, as a result of pressure generated from the drug release device, by diffusion, by electrodiffusion or by electroosmosis through the device and/or the catheter.

Gillis never operates as a closed loop or autonomous system controlled by local homeostatic parameters. Gillis' disclosed systems are all open loop systems and do not include an implanted control circuit to control said at least one piezoelectric pump to provide proper dosing and scheduling of said medicating agent in a closed loop control mode so that control of the operation of the system is performed autonomously with local homeostatic parameters as called for by amended claim 2. Reference is again made to the features of paragraphs [0007], [0010] and [0057], discussed above in connection with Kaiser and the distinctions noted there are reincorporated here.

Applicant respectfully requests advancement of the claims to allowance.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on December 20, 2006 by

_____
Signature

December 20, 2006

Respectfully submitted,

Daniel L. Dawes
Registration No. 27,123
Myers Dawes Andras
& Sherman LLP
19900 MacArthur Blvd., 11th Floor
Irvine, CA 92612
(949) 223-9600